CHRONIC TOXICITY SUMMARY

ACRYLONITRILE

(Acrylonitrile monomer, cyanoethylene, propenenitrile, 2-propenenitrile, VCN, vinyl cyanide.)

CAS Number: 107-13-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**5 µg/m^3** (2 ppb)
Critical effect(s)	Degeneration and inflammation of nasal epithelium in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Clear, colorless to pale yellow liquid (technical grades)
Molecular formula	C_3H_3N
Molecular weight	53.1 g/mol
Density	0.81 g/cm^3 @ 25^{o}C
Boiling point	77.3^{o}C
Melting point	–82^{o}C
Vapor pressure	100 torr @ 23^{o}C
Solubility	Soluble in isopropanol, ethanol, ether, acetone, and benzene
Conversion factor	1 ppm = 2.17 mg/m^3 @ 25 ^{o}C

III. Major Uses or Sources

Acrylonitrile is produced commercially by propylene ammoxidation, in which propylene, ammonia, and air are reacted by catalyst in a fluidized bed. Acrylonitrile is used primarily as a co-monomer in the production of acrylic and modacrylic fibers. Uses include the production of plastics, surface coatings, nitrile elastomers, barrier resins, and adhesives. It is also a chemical intermediate in the synthesis of various antioxidants, pharmaceuticals, dyes, and surface-active agents. Formerly, acrylonitrile was used as a fumigant for food commodities, flour milling, and bakery food processing equipment (HSDB, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3948 pounds of acrylonitrile (CARB, 2000). US EPA (1993) reported a mean ambient air concentration of acrylonitrile at four urban locations in the U.S.of 0.66 µg/m^3.

IV. Effects of Human Exposure

Many occupational epidemiology studies have investigated retrospectively the morbidity and mortality of acrylonitrile exposed workers. An increased incidence of lung cancer was associated with acrylonitrile exposure. No significant excess mortality has been observed for any noncarcinogenic endpoint. One early cross-sectional study (Wilson *et al.*, 1948) observed multiple deleterious effects in synthetic rubber manufacturing workers acutely exposed (20 to 45 minutes) to various concentrations of acrylonitrile (16 to 100 ppm, 34.7 to 217 mg/m^3). Mucous membrane irritation, headaches, feelings of apprehension, and nervous irritability were observed in the majority of workers. Other less common symptoms observed included low-grade anemia, leukocytosis, and mild jaundice. These effects were reported to subside with cessation of exposure. Human volunteers exposed for a single 8 hour period to acrylonitrile vapors exhibited no deleterious CNS effects at concentrations ranging from 5.4 to 10.9 mg/m^3 (2.4 to 5.0 ppm) (Jakubowski *et al.*, 1987).

A cross-sectional study (Sakurai *et al.*, 1978) found no statistically significant increases in adverse health effects in chronically exposed workers (minimum 5 years) employed at 6 acrylic fiber factories (n = 102 exposed, n = 62 matched controls). Mean acrylonitrile levels ranged from 0.1 to 4.2 ppm (0.2 to 9.1 mg/m^3) as determined by personal sampling. Although not statistically significant, slight increases in reddening of the conjunctiva and pharynx were seen in workers from the plant with the highest mean levels (4.2 ppm arithmetic mean). However, this study has limitations, including small sample size and examiner bias, since the medical examiner was not blind to exposure status. The time-weighted average exposure of the group occupationally exposed to 4.2 ppm (9.1 mg/m^3) acrylonitrile can be calculated as: TWA = 9.1 mg/m^3 x (10/20) m^3/day x 5 days/7 days = 3 mg/m^3. This level is comparable to the LOAEL (HEC) of 2 mg/m^3 derived by the U.S. EPA from the animal study of Quast *et al.* (1980).

Czeizel *et al.* (1999) studied congenital abnormalities in 46,326 infants born between 1980 and 1996 to mothers living within a 25 km radius of an acrylonitrile factory in Nyergesujfalu, Hungary. Ascertainment of cases with congenital abnormalities was based on the Hungarian Congenital Abnormality Registry plus review of pediatric, pathology and cytogenetic records. Particular attention was paid to indicators of germinal mutations (sentinel anomalies, Down's syndrome, and unidentified multiple congenital abnormalities) and to indicators of teratogens (specific pattern of multiple congenital abnormalities). Three congenital abnormalities: pectus excavatum in Tata, 1990-1992 (OR = 78.5, 95%CI = 8.4-729.6), undescended testis in Nyergesujfalu between 1980 and 1983 (8.6, 1.4-54.3) and in Esztergom, 1981-1982 (4. 2, 1.3-13.5) and clubfoot in Tata, 1980-1981 (5.5, 1.5-20.3) showed significant time-space clusters in the study area. The risk of undescended testis decreased with increasing distance from the factory. An unusual increase for the combination of oral cleft and cardiac septal defects was seen in multimalformed babies in Tatabanya in 1990. Unfortunately there were no data on levels of acrylonitrile or any other exposure.

V. Effects of Animal Exposure

Quast *et al.* (1980) exposed Sprague-Dawley rats (100/sex/ concentration) 6 hours/day, 5 days/week for 2 years to concentrations of 0, 20, or 80 ppm acrylonitrile vapors (0, 43, or 174 mg/m^3). A statistically significant increase in mortality was observed in the first year among 80 ppm exposed rats (male and female). Additionally, the 80 ppm exposed group had a significant decrease in mean body weight. Two tissues, the nasal respiratory epithelium and the brain, exhibited treatment-related adverse effects due to acrylonitrile exposure. Proliferative changes in the brain glial cells (i.e., tumors and early proliferation suggestive of tumors) were significantly increased in the 20 ppm (8/100) and 80 ppm (20/100) females versus female controls (0/100), and in the 80 ppm males (22/99) versus male controls (0/100). Noncarcinogenic, extrarespiratory effects were observed in the nasal turbinate epithelium at both exposure concentrations, 20 and 80 ppm (see table below). Thus the LOAEL was 20 ppm. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory epithelium were observed at either concentration.

Effects of acrylonitrile reported by Quast *et al*. (1980)

Effect	Sex	0 ppm	20 ppm	80 ppm
Respiratory epithelium hyperplasia in the nasal turbinates	Male	0/11	4/12	10/10*
Hyperplasia of the mucous secreting cells	Male	0/11	7/12*	8/10*
Focal inflammation in the nasal turbinates	Female	2/11	6/10	7/10*
Flattening of the respiratory epithelium of the nasal turbinates	Female	1/11	7/10*	8/10*
Lung: pneumonia, consolidation, atelectasis, or edema	Male	14/100	27/100*	30/100*
Lung: pneumonia, consolidation, atelectasis, or edema	Female	7/100	2/100	7/100

* statistically significant difference from controls ($p<.05$)

Maltoni and associates exposed Sprague-Dawley rats (30/sex/concentration) to 0, 5, 10, 20, or 40 ppm acrylonitrile vapor for 5 days/week over 52 weeks, and at 60 ppm for 4 to 7 days, 5 days/week for 104 weeks (Maltoni *et al.*, 1977; Maltoni *et al.*, 1988). Histopathologic examinations were performed, including on lungs, brain, kidney, and liver. No noncarcinogenic effects were reported.

Gagnaire *et al*. (1998) studied motor and sensory conduction velocities (MCV and SCV, respectively) and amplitudes of the sensory and motor action potentials (ASAP and AMAP) of the tail nerve in male Sprague-Dawley rats during chronic treatment with acrylonitrile. (Four other unsaturated aliphatic nitriles were also given orally to other rats.) Rats were given doses of 12.5, 25, and 50 mg/kg of acrylonitrile once a day, 5 days per week for 12 weeks. Rats were also exposed by inhalation to 25, 50, and 100 ppm of acrylonitrile vapors for 6 h/day, 5 days per week, for 24 weeks and neurophysiological examinations were carried out. After oral acrylonitrile, animals developed behavioral sensitization characterized by salivation, locomotor hyperactivity, and moderately intense stereotypies. Rats dosed with 50 mg/kg developed hindlimb weakness associated with decreases in sensory conduction velocity (SCV) and in the amplitude of the sensory action potential (ASAP). Rats exposed to acrylonitrile by inhalation exhibited time- and concentration-dependent decreases in motor conduction velocity (MCV), SCV, and ASAP, which were partially reversible after 8 weeks of recovery. The authors

concluded that the nervous system of the rat appears to be a target following either oral or inhalation exposures of acrylonitrile. The NOAEL by inhalation for 24 weeks was 25 ppm.

Changes in electrophysiological parameters after 24 wks of exposure (Gagnaire *et al*., 1998)

Acrylonitrile	MCV (m/sec)	SCV (m/sec)	AMAP (mvolts)	ASAP (μvolts)
0 ppm	42.9 ± 0.9[a]	53.3 ± 1.0	17.8 ± 1.2	186 ± 8
25 ppm	41.6 ± 0.8	50.5 ± 0.8*	16.1 ± 0.8	164 ± 11
50 ppm	38.1 ± 0.9**	49.1 ± 0.5***	15.7 ± 1.0	159 ± 5*
100 ppm	38.5 ± 1.2**	48.4 ± 1.0***	17.4 ± 0.9	133 ± 11***

[a] Mean ± SEM; * $p<0.05$; ** $p<0.01$; ***$p<0.001$

In a developmental study, Murray *et al.* (1978) exposed rats to acrylonitrile vapors at 0, 40 ppm (87 mg/m^3), or 80 ppm (174 mg/m^3) for 6 hours/day during gestational days 6 to 15. In the 80 ppm exposed group, significant increases in fetal malformations were observed including short tail, missing vertebrae, short trunk, omphalocoele, and hemivertebra (Murray *et al.*, 1978). No differences in implantations, live fetuses, or resorptions were seen in the exposed (40 and 80 ppm) versus the control group. Maternal toxicity was observed as decreased body weight at both exposure levels. After adjustment to continuous exposure, this study identified a developmental NOAEL of 10 ppm and a LOAEL of 20 ppm (with maternal toxicity).

Saillenfait *et al*. (1993) studied the developmental toxicity of eight aliphatic mononitriles in Sprague-Dawley rats after inhalation exposure for 6 hr/day during days 6 to 20 of gestation. The range of exposure levels for acrylonitrile was 12, 25, 50, and 100 ppm; group sizes were 20-23 females. Embryolethality was observed after exposure to 25 ppm (54 mg/m^3) acrylonitrile in the presence of overt signs of maternal toxicity. Fetal weights were significantly lower at 25 ppm. Thus 12 ppm (26 mg/m^3) is a NOAEL for developmental toxicity using this study design.

VI. Derivation of Chronic Reference Exposure Level

Study	Quast *et al.*, 1980
Study population	Sprague-Dawley rats (100/sex/concentration)
Exposure method	Discontinuous whole-body inhalation exposures (0, 20, or 80 ppm)
Critical effects	Degeneration and inflammation of nasal respiratory epithelium; hyperplasia of mucous secreting cells
LOAEL	20 ppm
NOAEL	Not observed
BMC_{05}	1.5 ppm
Exposure continuity	6 hours/day, 5 days/week
Average experimental exposure	0.27 ppm for BMC_{05} (1.5 x 6/24 x 5/7)
Human equivalent concentration	0.067 ppm (gas with extrathoracic respiratory effects; RGDR = 0.25 based on MV = 0.33 m^3/day, SA(ET) = 11.6 cm^2)

Exposure duration	2 years
LOAEL uncertainty factor	Not needed in the BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.002 ppm (2 ppb; 0.005 mg/m^3; 5 $\mu g/m^3$)

Sprague-Dawley rats (100/sex/concentration) were exposed 6 hours/day, 5 days/week for 2 years to 0, 20, or 80 ppm acrylonitrile (0, 43, and 174 mg/m^3, respectively). Significant degenerative and inflammatory changes were observed in the respiratory epithelium of the nasal turbinates at both exposure concentrations (20 and 80 ppm). This treatment-related irritation of the nasal mucosa appeared in the 20 ppm exposed male rats as either epithelial hyperplasia of the nasal turbinates, or as hyperplasia of the mucous secreting cells. In the 20 ppm exposed females it appeared as either focal inflammation in the nasal turbinates or flattening of the respiratory epithelium of the nasal turbinates. In 80 ppm exposed rats the effects were more severe, including suppurative rhinitis, hyperplasia, focal erosions, and squamous metaplasia of the respiratory epithelium. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory system were observed at either concentration. This study identified a LOAEL for pathological alterations in the respiratory epithelium of the extrathoracic region of the respiratory tract of 20 ppm (43 mg/m^3). The U.S. EPA (1994) based its RfC of 2 $\mu g/m^3$ on the same study but included a Modifying Factor (MF) of 10 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

OEHHA used a benchmark dose approach to determine the chronic REL for acrylonitrile. The cumulative gamma distribution model in the U.S. EPA's BMDS sotware was individually fit to the data on respiratory epithelium hyperplasia in the nasal turbinates in males, hyperplasia of the mucous secreting cells in males, focal inflammation in the nasal turbinates in females, and flattening of the respiratory epithelium of the nasal turbinates in females. The resulting BMC_{05} values (1.27, 1.33, 2.18, 1.35) were averaged to yield a value of 1.5 ppm. The RGDR adjustment and appropriate uncertainty factors were applied as indicated in the above table and resulted in a chronic REL of 5 $\mu g/m^3$.

For comparison, Gagnaire *et al*. (1998) found a NOAEL for nervous system effects at 24 weeks of 25 ppm, which is equivalent to a continuous exposure of 4.5 ppm. Use of the default RGDR of 1 for systemic effects, a subchronic UF of 3, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 45 ppb (100 $\mu g/m^3$). We were unable to derive a BMC from the neurotoxicity data due partly to the tendency of the animals in the 100 ppm group to yield values for two of the four endpoints measured closer to the controls than those in the 50 ppm group.

As another comparison, Saillenfait *et al*. (1983) found a 12 ppm (26 mg/m^3) NOAEL for fetal weight reduction (6 h/d exposure). This is equivalent to a continuous exposure of 3 ppm (on

days 6 to 20 of gestation). Use of the default RGDR of 1 for systemic effects, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 100 ppb (200 $\mu g/m^3$).

Finally, after adjustment to continuous exposure, Murray *et al*. (1978) identified a developmental NOAEL, adjusted to continuous exposure, of 10 ppm and a LOAEL of 20 ppm (with maternal toxicity at both levels). Use of the default RGDR of 1 for systemic effects, an interspecies UF of 3, and an intraspecies UF of 10 results in an estimated REL of 30 ppb (70 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the chronic REL for acrylonitrile include (1) the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis and (2) the demonstration of a dose-response relationship. Major uncertainties are (1) the lack of adequate human exposure data, (2) the lack of a NOAEL in the 2 year study, (3) lack of inhalation bioassay in a second species, and (4) lack of reproductive data for inhalation exposures when an oral study showed adverse reproductive effects

When assessing the health effects of acrylonitrile, its carcinogenicity must also be assessed.

VIII. Potential for Differential Impacts on Children's Health

The chronic REL is considerably lower than the comparison estimate based on developmental effects. Although neurotoxicity, an endpoint which is often associated with increased sensitivity of younger animals or humans, was evaluated as one of the alternative endpoints, the comparison reference level for this end point in adults was more than an order of magnitude higher that the REL based on histological changes in the upper respiratory tract. It is therefore considered that the REL is likely to be adequately protective of infants and children.

IX. References

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